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(54) **Title:** SKIN PRODUCT HAVING MICRO-SPHERES, AND PROCESSES FOR THE PRODUCTION THEREOF

(57) **Abstract:** Processes for preparing Skin and/or wound and burn care compositions and/or phase stable emulsions comprising one or more of the following; organic base salts of fatty acids, fatty esters, fatty alcohols, non-ionic and quartemary ammonium surfactants, and other highly polar compounds, a liquid carrier, and optionally one or more active agents. The compositions and/or phase stable emulsions contain fatty microspheres. The compositions that are especially adapted to topically deliver active and/or medicinal agents to the surface of the skin, burns, skin lesions, warts, and ulcers.

SKIN PRODUCT HAVING MICRO-SPHERES, AND PROCESSES FOR THE PRODUCTION THEREOF.

RELATED APPLICATIONS

This application claims priority to United States Patent Application Serial No. 09/755,607, filed January 05, 2001.

FIELD OF THE INVENTION

This invention relates generally to skin products, and particularly to emulsion-based skin products that can be applied to the skin to provide continuing antimicrobial, antiviral, antiseptic, and skin protecting or healing properties.

BACKGROUND OF THE INVENTION

People often use soaps and bactericides to remove and exterminate undesirable contaminants such as dirt and bacteria from the skin, especially the hands. These products are typically applied to the skin while washing the hands under running water. The products have a limited temporal effect, however, because they are washed from the skin along with the dirt and bacteria during the washing process. Conventional soaps and bactericides do not, therefore, provide any lasting effect after they have been used. However, in many occupations, such as the medical profession, it is important to minimize and destroy harmful bacteria and viruses immediately when they contact the skin. A skin product that provided continued protection against contaminants with which the skin comes into contact, after being applied to the skin, would therefore be highly desirable. Such skin products should be specifically formulated for the special demands of particular applications.

In some applications, the need for rapid and anti-bacterial and anti-viral activity is particularly important. For example, surgeons and medical care practitioners require surgical scrub products that sanitize their hands before surgery or like procedures. FDA requires these products to have increasing efficacy the longer they are used. That is, regulations require that surgical scrub products improve their performance versus basic soaps with repeated use.

Prior art surgical scrub products are harsh to the hands. A typical surgical scrub product contains over 60% ethyl alcohol. Those products are very effective at killing

microorganisms, but are equally effective at removing skin oils that make the skin soft and substantially crack-free. When hands are cracked and sore, it is more difficult to perform delicate surgery.

A product that matched the rapid anti-microbial behavior of high-alcohol surgical scrubs, by use of formulations containing aggressive anti-microbial agents, but which simultaneously coated and protected the medical practitioner's hands would be especially valuable.

Nevertheless, some skin is so damaged that aggressive anti-microbial active ingredients are too irritating for use in skin-care products. People who have developed a latex intolerance are typical of this group, because allergic reactions to the proteins or other irritants in latex products make their hands red and sore to the point of bleeding. Such allergies can threaten the careers of health care practitioners. If a skin-care product could be formulated to form a layer that coated, soothed, and protected the skin, yet could serve as a protective base layer for additional layers containing anti-microbial active agents, health care practitioners could protect themselves from harmful latex proteins, yet protect their patients from pathogenic organisms.

A different special situation is presented for skin products formulated for children younger than six years old. This population has a well documented history of frequent infections, many of which are transmitted via the hands. Children often have fingers and such in their mouths, so special formulations are required to make a safe and effective skin protectant product for children. A product that could protect and simultaneously disinfect the hands of young children, but be safe for them to occasionally ingest would improve the health of this special population.

Another special situation is baby's bottoms. Babies are prone to diaper rash and the like. A product that was gentle to baby's skin, yet protected this tender skin from the bacteria of feces and urine would be of particular advantage.

A skin-care product could also be adapted to topically deliver active agents, such as drugs, continuously to wounded, burned or ulcerated skin, or skin otherwise lacking in normal integrity. For example, preparations for removing warts might purposefully deliver toxic or irritating agents to selected areas of wounded skin.

Yet another set of special situations is presented by skin-care products formulated to topically deliver medicinally active agents to burns and wounds. Optimum wound or burn care products should (1) reduce inflammation by delivering anti-inflammatory agents or biological precursors of anti-inflammatory agents, (2) provide necessary nutrients and building block precursors for the biologically produced prostaglandin, leucotriene, and thromboxane compounds which regulate inflammation and promote tissue healing or new skin growth at a burn site which may have impaired blood supply, (3) promote normal and/or healing microbial activity at the wound surface, yet inhibit outside infections caused by external pathogenic bacteria or viruses, and (4) optionally modify electrical charge density in and around the wound so as to attract biologically provided nutrients and building block precursors to the wound site, which may have a deficient blood supply.

It would be especially desirable to formulate products for the treatment of wounds, or thermal, chemical, or radiation burns, to accomplish the above-described functional objectives. It would be desirable to formulate a composition which promotes increased levels of biosynthesized prostaglandin hormones such as PGE1, PGE3, PGI2, which promote healing of damaged skin and tissue, and caused decreased levels of prostaglandin PGE2, which produces undesirable inflammatory responses at a wound site. It would also be desirable to provide building block precursors of the hormones and other necessary cellular components, such as vitamins, minerals, sulfur compounds, saturated and unsaturated fatty acids, neurotransmitters, anti-oxidants, and other compounds which promote healing.

Prior art products provide anti-inflammatory compounds, necessary nutrients, or antiseptic treatments followed by non-sterile conditions, but none of the prior art teaches combining all the above functions in one stable salve.

Of particular importance is the healing of wounds and decubitus ulcers. A decubitous ulcer often begins as a bed shearing force abrasion on an immobilized patient. Body pressure restricts blood flow where the skin is in contact with the mattress. Necrosis ensues within 30 minutes, and a Level 1 ulcer (bed sore) develops. In more severe cases, the epidermal layer is disrupted (for example by scratching) and bacteria enter the site. As

the ulcer severity increases, a deep sore opens up in a conical fashion. In a Level 4 decubitous ulcer, the bone is often visible.

Prior art treatments of Level 4 decubitous ulcers first require sanitizing the wound to kill pathogenic micro-organisms, as well as normally benign or beneficial micro flora. Medicines were subsequently applied to the sanitary wound, or heavy debridement of damaged tissue was repeatedly applied during prior art treatments. Healing is problematic using such treatments, typically taking 6 months, and is successful less than half the time.

Improved compositions and methods for successfully treating such ulcers within 1-2 months would substantially advance the art. Indeed, improved compositions and methods for treating thermal burns, radiation burns, surface wounds, deep wounds or ulcers, warts, or diaper rash would substantially advance the medical arts.

SUMMARY OF THE INVENTION

In accordance with the purpose(s) of this invention, as embodied and broadly described herein, this invention, in one aspect, relates to a method of treating or preventing ailments of the skin, comprising applying to the surface of animal skin or tissue an effective amount of a composition capable of forming a film that ionically bonds to the skin or tissue comprising the residue of: one or more active agents; a nonionic or substantially nonionic first film forming component; one or more cationic surfactants comprising one or more fatty moieties that are soluble in the first film forming component; and a liquid carrier.

In another aspect the invention provides a method of treating or preventing skin ailments comprising applying to the surface of animal skin or tissue an effective amount of a composition comprising the residue of: one or more quaternary ammonium compounds; one or more surfactants; one or more fatty esters; one or more fatty alcohols; and optionally one or more highly polar compounds; wherein the ratio of the sum of the moles of quaternary ammonium compounds, surfactants, and highly polar compounds to the sum of the moles of fatty esters and alcohols is from about 0.8 to about 1.2.

In still another aspect the invention provides a method of treating or preventing skin ailments comprising applying to the surface of animal skin or tissue an effective amount of an emulsion composition comprising the residue of a fatty phase, wherein: the

fatty phase comprises fatty acids, glycerides, and optionally other fatty components, and the molar ratio of fatty acids to glycerides and other fatty components is from about 0.5 to about 5.5.

Additional aspects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawing, which is incorporated in and constitute a part of this specification, illustrates several embodiments of the invention and together with the description, serve to explain the principles of the invention.

Figure 1 shows estimated volume of a patient's heel wound versus time in days, wherein the wound was undergoing treatment with the methods and compositions of the inventions, as disclosed in Example 15.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the Examples included therein.

Definitions and Use of Terms

Before the present compounds, compositions and methods are disclosed and described, it is to be understood that this invention is not limited to specific synthetic methods, or to specific formulations or administration regimens, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a fatty ester" includes mixtures of

fatty esters, reference to "a liquid carrier" includes mixtures of two or more such carriers, and the like.

It must also be noted that ingredients in the claimed compositions can be referred to by more than one term, because of the multiple functions that these ingredients perform. Thus, ascorbyl palmitate acts as both a film forming stabilizer an antioxidant, and vitamin; as do vitamin E and beta-carotene. Other examples include EPA, CLA, DHA, and GLA which act as prostaglandin stimulators, precursors to prostaglandins, and also stabilize the final film, and facilitate the migration of medicinals through this film, and thus to the skin; thereby enhancing the medicinal's topical absorption. All of the previously mentioned are considered fatty moieties of the final film. Another example is dimethyl benzethonium chloride which acts as an antimicrobial, and also enhances wound healing by modifying the charge at the wound site. Another example is the adduct of a nitrogenous organic base and a fatty acid, which can function both as an active agent and a constituent of a film forming component. A final example is arginine, and other amino acids which act as neurotransmitters which stimulate the healing process and also are nutrients for use at the wound site. Complexed minerals such as zinc sulphate and copper curcumin act as antimicrobials, antifungals and also provide nutrition to the wound for speedier healing.

Ranges are often expressed herein as from about one particular value, and/or to about another particular value. When such a range is expressed, it is to be understood that a more preferred range is typically from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about", will be understood that the particular value is typically more preferred. It will further be understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

References in the specification and concluding claims to parts by weight, of a particular element or component in a composition or article, denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a composition containing 2 parts by weight of component X and 5 parts by weight component Y, X and

Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the composition.

A residue of a chemical species, as used in the specification and concluding claims, refers to the moiety that is the resulting product of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more $-OCH_2CH_2O-$ units in the polyester, regardless of whether ethylene glycol was used to prepare the polyester. Similarly, a residue of NaCl in solution, under appropriate conditions, refers to the sodium anion and chloride cation in solution.

The term "alkyl" as used herein refers to a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, octyl, decyl, tetradecyl, hexadecyl, eicosyl, tetracosyl and the like. The term "lower alkyl" intends an alkyl group of from one to six carbon atoms, preferably from one to four carbon atoms. The term "cycloalkyl" intends a cyclic alkyl group of from three to eight, preferably five or six carbon atoms.

The term "alkoxy" as used herein intends an alkyl group bound through a single, terminal ether linkage; that is, an "alkoxy" group may be defined as -OR where R is alkyl as defined above. A "lower alkoxy" group intends an alkoxy group containing from one to six, more preferably from one to four, carbon atoms.

"Surface" of skin or tissue means the exposed area of skin or tissue associated with a skin ailment, and thus can be below the level of surrounding skin or tissue for deep wounds, ulcers, and other ailments.

"Ailments of the skin" refers to skin disorders, and include, for example, skin lesions, wounds, ulcers, burns, radiation burns, diaper rash, blisters, acne, psoriasis, athlete's foot, and warts.

The term "debridement" as used herein refers to a procedure used in the treatment of burns, wounds, and ulcers, wherein the burn, wound, or ulcer is subjected to vigorous mechanical or pharmaceutical cleaning and/ or sterilization, which can include treatment with strong anti-microbial agents, or cutting away scabs and dead or damaged tissue.

The term "burn" as used herein refers to tissue injury resulting from excessive exposure to thermal, chemical, electrical, or radioactive agents, or electromagnetic radiation.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not. For example, the phrase "optionally substituted alkyl" means that the alkyl group may or may not be substituted and that the description includes both unsubstituted alkyl and alkyl where there is substitution.

By the term "effective amount" of a compound or property as provided herein is meant such amount as is capable of performing the function of the compound or property for which an effective amount is expressed. As will be pointed out below, the exact amount required will vary from process to process, depending on recognized variables such as the compounds employed and the processing conditions observed. Thus, it is not possible to specify an exact "effective amount." However, an appropriate effective amount may be determined by one of ordinary skill in the art using only routine experimentation.

Discussion

The invention is a creme or lotion composition that is especially effective for treating or preventing skin related ailments. The composition, when applied to the skin, provides a protective film that promotes skin healing, and which can be modified to topically deliver medicinal ingredients.

The composition has several novel aspects. Thus, in one embodiment the invention provides a method of treating or preventing ailments of the skin, comprising applying to the surface of animal skin or tissue an effective amount of a composition capable of forming a film that ionically bonds to the skin or tissue comprising the residue of one or more active agents; a nonionic or substantially nonionic first film forming component; one or more cationic surfactants comprising one or more fatty moieties that are soluble in the first film forming component; and a liquid carrier.

In another aspect the invention provides a method of treating or preventing skin ailments comprising applying to the surface of animal skin or tissue an effective amount of a composition comprising the residue of: one or more quaternary ammonium

compounds; one or more surfactants; one or more fatty esters; one or more fatty alcohols; and optionally one or more highly polar compounds; wherein the ratio of the sum of the moles of quaternary ammonium compounds, surfactants, and highly polar compounds to the sum of the moles of fatty esters and alcohols is from about 0.8 to about 1.2.

. In still another aspect the invention provides a method of treating or preventing skin ailments comprising applying to the surface of animal skin or tissue an effective amount of an emulsion composition comprising the residue of a fatty phase, wherein: the fatty phase comprises fatty acids, glycerides, and optionally other fatty components, and the molar ratio of fatty acids to glycerides and other fatty components is from about 0.5 to about 5.5. In separate embodiments the molar ratio is from about 0.5 to about 3.5, and from greater than about 3.5 (i.e. above the range encompassed by "about 3.5) to about 5.5.

From about 20 to about 40 parts by weight of one or more active agents are typically present in the composition, although from about 25 to about 35 parts by weight are preferred. The ingredients that make up the first film forming component typically comprise from about 1 to about 5 parts by weight of the total composition, and preferably comprise from about 2 to about 4 parts by weight. The composition typically comprises from about 0.2 to about 5 parts by weight of cationic surfactant, and preferably comprises from about 1 to about 3 parts by weight cationic surfactant. From about 50 to about 80 parts by weight of the liquid carrier are typically present in the composition, although from about 60 to about 75 parts by weight are especially preferred.

The first film forming component is preferably insoluble in the liquid carrier, and present in the composition as an emulsion. When applied to the skin, the first film forming component forms a hydrophobic film that covers the skin as the liquid carrier evaporates. The hydrophobic film provides a suitable environment for skin or tissue to heal. By bonding to the skin, the film can also exclude water and harmful agents such as bacteria from the surface of the skin.

The hydrophobic film may also act as a foundation for imparting continuing properties to the skin. Antiviral and antibacterial agents can be incorporated into the film, and thereby provide residual protection against contaminants with which the skin may

come into contact. The hydrophobic film may also act as a medium through which medicinal agents can migrate and be delivered to the skin.

The hydrophobicity of the film can, of course, vary. However, the film is preferably sufficiently hydrophobic, and the film forming component sufficiently insoluble, to exclude water (and dissolved active ingredients such as cleansers and bactericides) from the surface of the skin as a film is formed on the surface of the skin. The film that is formed is preferably sufficiently impervious to water to minimize the incidence of water (which can carry aggravating cleansers, bacteria and other undesirable constituents) migrating through the film barrier.

Numerous formulations can be used as the first film forming component. For example, the first film forming component can include natural and synthetic polymers and waxes. For reasons that will become apparent, preferred formulations solubilize fatty moieties, and can selectively incorporate fatty moieties from ionic compounds within their structure, while excluding other ionic moieties from the compound, upon drying to form a film. Waxes, which contain the esters of fatty acids and fatty alcohols (other than glycerol), are especially suitable ingredients for the first film forming component. Waxes that suitably interact with propolis to impart the desired properties to the film are especially preferred.

An especially suitable formulation for the first film forming component comprises natural or synthetic bees wax; propolis; one or more fatty acids; and one or more fatty alcohols. Fatty refers generally to high molecular weight aryl, aliphatic, cycloaliphatic, saturated or unsaturated, straight or branched aliphatic compounds, preferably saturated and/or aliphatic and/or straight The fatty acids and fatty alcohols typically comprise greater than 10 or 12 carbon atoms, and/or less than 32, 26, or 18 carbon atoms. Thus, in one embodiment the fatty acid comprises from about 10 to about 32 carbon atoms, and the fatty alcohol comprises from about 10 to about 32 carbon atoms. In a preferred embodiment the fatty acid comprises from about 12 to about 18 carbon atoms, and the fatty alcohol comprises from about 12 to about 16 carbon atoms. In an even more preferred embodiment, the fatty acid comprises stearic acid, and the fatty alcohol comprises cetyl alcohol or myristic alcohol. In addition to being an integral element of the film, the fatty

acid also preferably acts as a surfactant after it has been neutralized. The fatty alcohol preferably acts as an emulsifying agent. The alcohol can be substituted with groups such as amides, alkyl, and allyl groups, to tailor the alcohol to a specific set of requirements.

The bees wax is preferably natural, with crude, filtered bees wax being especially preferred. The bees wax can, however, be synthetic, or substituted with other natural waxes, as long as the wax possesses a net positive charge and a chemical similarity to natural bees wax, and interacts favorably with propolis. A particularly suitable synthetic bees wax is the synthetic wax manufactured by Alzo, Inc. of Sayreville, NJ, under the trade name Waxenol-8-22 (arachidyl behenate).

The propolis may preferably comprise propolis wax or propolis resin. The propolis may constitute a distinct ingredient of the composition, or it may be added as part of another ingredient such as the bees wax. The weight ratio of propolis to bees wax preferably meets or exceeds the ratio at which propolis and bees wax naturally occur (about 26:74).

The first filming component may optionally further comprise the solution residue of a monoester monoglyceride. The acidic residue of the monoester monoglyceride preferably comprises from about 10 to about 18 carbon atoms, and most preferably comprises 12 carbon atoms. The monoglyceride may be unsaturated, and may have up to three double bonds. Saturated monoglycerides are, however, especially preferred. The monoglyceride may also be substituted with, for example, one or more alkyl groups, especially the lower alkyl groups. A particularly suitable monoglyceride is lauricidin (distilled glyceryl monolaurate).

The first film forming component typically comprises from about 1 to about 12 parts by weight monoester glyceride, from about 0.2 to about 3.0 parts by weight bees wax, from about 0.1 to about 1.5 parts by weight propolis, from about 1.5 to about 10 parts by weight of one or more fatty acids, and from about 1 to about 8 parts by weight one or more fatty alcohols, independently or in combination. The first film forming component preferably comprises from about 2 to about 6 parts by weight monoester glyceride, from about 0.5 to about 1.5 parts by weight bees wax, from about 0.2 to about 0.6 parts by weight propolis, from about 3 to about 5 parts by weight of one or more fatty acids, and

from about 2 to about 4 parts by weight of one or more fatty alcohols, independently or in combination.

The composition also preferably comprises a cationic surfactant, preferably comprising one or more fatty moieties. It is believed that the cationic surfactant binds ionically to the anionic sites on the surface of the skin, and, because the fatty moieties from the cationic surfactant are solubilized in the first film, anchors the film to the skin. It is also believed that the surfactant, by drawing the film toward the skin, helps to exclude water from the surface of the skin. The surfactant is preferably sufficiently cationic to achieve this anchoring function. Similarly, the fatty moieties preferably are sufficiently soluble and large, and have sufficient interaction with the film, to achieve this anchoring function. For example, fatty moieties comprising from about 12 to about 22 carbon atoms, and especially fatty moieties comprising about 18 carbon atoms, are most preferred.

The cationic surfactant preferably makes up at least 0.10 wt. % of the composition, and preferably comprises no more than about 5.0 wt. % of the composition. Less cationic surfactant than 0.10 wt. % is not evenly distributed across the surface of the film, and therefore is not as effective to evenly bond the film to the skin, and uniformly exclude water from the surface of the skin. More cationic surfactant exceeds current FDA regulations.

In one embodiment the fatty cationic surfactant of the composition comprises an ammonium compound that is substituted with at least one lower alkyl moiety. In another embodiment the ammonium compound is substituted with from one to three lower alkyl moieties, and one or more fatty moieties comprising from about 8 to about 22 carbon atoms, preferably from about 16 to about 22 carbon atoms. The fatty moiety can preferably be aryl, aliphatic, cycloaliphatic, saturated or unsaturated, straight or branched. In a more particular embodiment the cationic surfactant comprises the solution residue of dimethyl distearyl ammonium chloride. A dimethyl, ditallow ammonium chloride residue, with its broader molecular weight distribution, is also preferred.

The liquid carrier for the composition can also vary. Indeed, any carrier that does not substantially interfere with the components or the function of the components, and which allows a film to form and thereby exclude the carrier from the skin surface as it

evaporates, is suitable. Exemplary carriers include water, and lower molecular weight alcohols such as ethanol, isopropyl alcohol, sec-butyl alcohol, glycerin, and propylene glycol, although water is generally preferred for the particular ingredients described in this document.

The composition may comprise one or more active agents, which are chosen based upon the properties that one desires from the composition. For example, in one embodiment the composition may include an aggressive cleansing or skin preparation ingredient. Such active agents cleanse the surface of the skin immediately upon application of the composition to the skin, and cleanse the skin sufficiently before a film is formed from the first film forming component, and before the first film forming component excludes the active agents from the surface of the skin.

Cleansing ingredients may be capable of removing microbials, viruses, and other foreign contaminants from the surface of the skin. Cleansing ingredients may also be capable of scouring dead and dying layers of skin from the skin surface. The cleansing ingredient may suitably comprise non-ionic surfactants because:(1) this class of compounds readily cleanses the skin, and removes the fatty dead, and dying layers of the outer surface of the skin (the stratum disjunction and stratum corneum); (2) this class of compounds is typically very soluble in the water base of the composition; (3) this type of compound is an effective antiviral compound; and (4) this class of compounds allows the proper functioning of the other active ingredients of the composition.

Surfactants are particularly suitable because of their ability to cleanse at the interface of the liquid composition and the outer layers of the skin. A particularly suitable nonionic surfactant is sold under the trade mark Triton X-100, and comprises octoxylenol, most suitably having 9-10 repeating units of ethoxylation. Another particularly suitable nonionic surfactant is nonoxynol-9, which can be used alone or in combination with other surfactants.

Suitable antimicrobial and cleaning active agents that can be incorporated into the composition include propylene glycol, berberine sulfate, various quaternary ammonium compounds, such as dimethyl benzethonium chloride, benzalkonium chloride, benzoxonium chloride, and cetyl pyridinium chloride. Additional antimicrobial and

cleansing agents include, but not limited to parachlorometaxylenol, nonoxynol-9, chlorohexadine gluconate, and lauricidin (glycerol monolaurate). Other active agents include skin healing emollient ingredients such as allantoin, aloe, dimethyl sulfone, dimethicone, fragrances and anti-oxidants.

It is also possible to include active agents with medicinal properties in the composition which, when delivered topically, are absorbed by the skin and metabolized. Any active agent that is fat soluble, or which can be rendered fat soluble, is a suitable candidate for delivery through the compositions of the present invention, because such agents are capable of migrating through the final film formed by the composition, and thereafter being topically delivered to the skin.

The medicinally active agents of the invention can be added singly, or in any combination. Each medicinally active agent typically comprises from about 0.01 weight % to about 3.0 weight percent of the composition, although active agents can be present, either singly or in combination, in quantities as high as 25 wt.%, 20 wt.%, 15 wt.%, 10 wt.%, or 5 wt.%. Most medicinally active agents are preferably present from about 0.01 weight % to about 1.0 weight percent. Preferred medicinally active agents include alkylglycerols, alkoxyglycerols, polyunsaturated fatty acids or polyunsaturated oils, fat soluble vitamins, sulfur compounds, minerals, antioxidants, amino acids, energy stimulators, steroidal hormones, or glycoprotein hormones. Preferred medicinally active agents also include a variety of other healing agents including glycyrrhizic acid, ribonucleic acids, aloe vera, allantoin, bioperine, berberine hydrochloride, colostrum, dexpanthenol, glucosamine salts, inositol, phytantriol, pyrolidine carboxylic acid, jojoba oil, symphytum officinal, polysorbate 80, vanilla extract, and adducts of a nitrogenous organic base and a fatty acid. Adducts of nitrogenous organic bases and fatty acids are especially appropriate for use in higher concentrations.

Glycerides, including mono-, di-, and triglycerides, and alkoxyglycerols and alkylglycerols, are particularly suitable as active agents, or as carriers for active agents, in topical applications. These components have independent medicinal properties, are capable of independently migrating through the film, and can also solubilize other fat soluble active agents and carry them through the first film to the surface of the skin.

Particularly suitable glycerides typically comprise from about 10 to about 36 carbon atoms, can be conjugated or saturated, and are generally liquid at room temperature. Preferred glycerides include, lauricidin, vitamin D suspended in palm oil, conjugated linoleic acid ("CLA"), gamma linolenic acid ("GLA"), and eicosapentaenoic acid (EPA). Highly unsaturated oils are also especially suitable active agents in such topical applications because such oils have an antioxidant benefit when applied to the skin, and in addition they are effective transport vehicles for fat soluble active agents.

The polyunsaturated fatty acids used as medicinally active agents include conjugated linolenic acid, alpha-linolenic acid, alpha-linoleic acid, gamma linolenic acid, dihomo-gamma-linolenic acid, docosahexaenoic acid, eicosapentaenoic acid. The polyunsatured fatty oils useful in the invention include neem oil, shark liver oil, lemon oil, or squalene. Other fatty oils include lemon oil and squalane. Shark liver oil and /or neem oil are typically used at higher concentrations than other medicinally active agents, and are thus typically present at concentrations of up to 10, 5, or 3 wt.% of the composition.

Preferred fat soluble vitamins include vitamin A, vitamin D, vitamin E, vitamin K, a tocotrienol, lycopene, b-carotene, ascorbyl palmitate, and luteine. Preferred sulfur compounds include dimethylsulfone, zinc sulfate, or lipoic acid. Preferred minerals include zinc sulfate; zinc l-monomethionine; and compounds of copper, calcium, magnesium, chromium, selenium, vanadium, cobalt, and silica. Compounds include salts and chelates, among others, and especially include calcium proprionate; copper porphyrin compounds, silicic acid or silica gel, and copper-curcumin.

Preferred anti-oxidants include ascorbyl palmitate, neem oil, squalene, ferulic acid, lipoic acid, grape seed extract, boswellin, lycopene and bilberry extract. Preferred amino acids include arginine, proline, glutamine, glycine, or trimethyl glycine, ornithine alpha-ketoglutarate, and l-pyrroglutamic acid.

Energy stimulators are defined as compounds that provide easily metabolized sources of energy for the synthesis of ATP, and include bee pollen, natural honey, forskholin, and arginine. Preferred steroid hormones include cortisol, pregnenolone, and dehydroepiandrosterone .

Another class of active agents include optically flourescent or phosphorescent compounds or compositions that can absorb ultraviolet light and re-emit it as visible light. When hands or other skin surfaces that have been treated with the resulting flourescent or phosphorescent compositions, exposure to a source of ultra-violet ("black") light can be used as a method to check for the presence of the composition on the skin. This property might be particularly useful in skin cleaning and/or skin protecting compositions utilized in hospital, food manufacturing, or food service facilities, as a means for easily checking for the presence of the cleaning or skin protecting composition.

When the composition is used to deliver medicinal active agents, the composition may preferably be modified by the addition of a suitable partitioning agent. Such partitioning agents preferably comprise from about 0.1 to about 3.0 wt. % of the composition, and even more preferably comprise from about 0.3 to about 1.5 wt. % of the composition. Partitioning agents can be incorporated in the composition in order to (1) facilitate the migration of active agents through the film, and (2) modulate the skin surface to facilitate penetration of the skin by the active agents. Suitable partitioning agents include carbomers, hydroxymethylcellulose, and glyceridyl monooleate, as taught, for example, by Ogiso et al., in J. Pharm. Sci. 84:482-488 (1995), by Roy et al., in Int'l Jnl of Pharm. 110:137-145 (1994), and by Niazy et al., in AAPS 9th Ann. Mtg. Abst. 7080. Pharm Res. 11:5194 (1994), the disclosure from the above references being hereby incorporated by reference.

A particularly effective class of partitioning agents for use with the compositions of the present invention are the nonionic polyethoxylated fatty ethers and alcohols. The molecular weight of these agents, and their limited solubility in the liquid carrier, cause them to form a layer on the surface of the skin even before the first film forming component forms a film. After the film has formed, it is believed that these agents interact with the cationic surfactants that are anchored to the film in a manner that facilitates the transmission of active agents from the film into the skin. Moreover, the ethoxylation of the compounds appears to minimize and prevent undue irritation of the skin by these surfactant compounds. The degree of ethoxylation also appears to affect the rate at which active agents are partitioned by the partitioning agent.

The effectiveness of the partitioning agent at facilitating the transmission of an active agent varies depending upon the size and polarity of the active agent. In general, the size of the active agent and the size of the partitioning agent are directly related, so that larger active agents require larger partitioning agents. The degree of ethoxylation of the partitioning agent is also directly related to the size of the active agent and the polarity of the active agent.

The degree of ethoxylation of the partitioning agent typically ranges from about 10 to about 400 units of ethoxylation, although it preferably ranges from about 10 to about 100 units of ethoxylation, and most preferably ranges from about 10 to about 20 units of ethoxylation. The size of the partitioning agent typically ranges from about 12 to about 36 carbon atoms, and preferably ranges from about 12 to about 18 carbon atoms. Particularly suitable partitioning agents include polyoxy(10)O-ethanol and ceto stearyl alcohol.

The composition may also comprise one or more anionic surfactants having one or more fatty moieties that are soluble in the first film forming component. The fatty acids that comprise the first film forming component are typically neutralized during preparation of the composition, and are especially suitable anionic surfactants. These surfactants are believed to be capable of forming a substantially discreet layer in the dried structure on the skin. Due to the unique structures of these anionic surfactants, they are capable of anchoring in the film through their fatty moieties, with their anionic portion being typically oriented on the opposite side of the film from the skin (because the anionic charge is repelled by the anionically charged skin surface). Because the anionic surfactant is located on the exposed side of the film, and is anchored in the film through its fatty moieties, the surfactant imparts continuing properties to the film. In a preferred embodiment the fatty moieties of the anionic surfactant comprise from about 12 to about 22 carbon atoms. A preferred anionic surfactant is a salt of stearic acid or sodium lauryl sulfate.

In another embodiment the composition comprises a nitrogenous organic base. The base stabilizes the emulsion when the composition comprises an emulsion, although how such stabilization is achieved is not well understood. The base is preferably triethanolamine, tromethamine, or a tris amino alcohol compound such as tris(hydroxymethyl)aminomethane, tris(hydroxymethyl)aminoethane, with triethanolamine

and tromethamine being especially preferred. The nitrogenous base preferably forms an adduct with the fatty acid in the first film forming component. In a preferred embodiment the first film forming component is modified with a fatty acid/nitrogenous base adduct formed by mixing the fatty acid with one or more nitrogenous bases at temperatures between about 57 and about 80 C. Such adduct, in combination with the cationic surfactant, make at least one side of the first film essentially lipophilic and positively charged, and thereby attracted by the negatively charged skin.

Other ingredients may be included in the composition. Tetra sodium EDTA, for example, is preferably added to the composition in order to partially neutralize an emulsion of the composition. EDTA may also sequester any hard components of the water and further reduce the potential for any negative interactions between the hard components of the water and the active ingredients of the composition. From about 0 to about 0.5 parts by weight of EDTA are typically employed. A thickener can also be added to the composition in order to increase its viscosity, and obtain a creme product suitable for applying and rubbing into skin. Particularly suitable thickening agents include carboxypolymethylene (carbopol) and sodium carboxymethyl cellulose, present in the composition at from about 0 to about 0.6 parts by weight. Other ingredients that can be included in the composition include process aids such as glycerin and propylene glycol, emulsion stabilizers for the stearic acid such as cetyl alcohol, and preservatives such as chlorohexadine gluconate.

Additional ingredients can be added to the composition to build upon the layering effect of the composition, and to provide additional properties to the composition. In particular, in order to improve the residual properties of the composition, an outer film-forming component can be added to the composition. The outer film-forming component can be comprised of ingredients that form a substantially discreet film after the hydrophobic first film has formed, and therefore which surrounds the hydrophobic film. If properly formulated, the outer film traps and encapsulates active agents that may be contained in the composition.

Although other film-forming ingredients will be apparent to workers skilled in the art, a particularly suitable outer film forming ingredient is polyvinyl pyrrolidine (PVP),

because it is initially soluble in water, but becomes insoluble upon drying and forming a film. It is believed that PVP, which can be added to the composition as a waxy non-soluble phase, coalesces and forms an outer film after the hydrophobic film has formed. It is believed that the outer film forms after the hydrophobic film has formed because the hydrophobic film forming ingredients respond more quickly to the evaporation of water from the composition and the resultant concentration of non-water ingredients in the composition. In essence, the hydrophobic film components are less soluble than the outer film ingredients and therefore precipitate first as water from the composition evaporates. Some of the active agents become entrapped between the hydrophobic film and the PVP outer film, it is further believed, because these active agents effectively precipitate from solution after the hydrophobic film has formed but before the outer film has coalesced. Because nonionic surfactants are the most soluble component of the composition, the outer film probably coalesces before the non-ionic surfactants precipitate from solution, and the outer film probably excludes and expels any non-ionic surfactants further from the skin, where they can provide desired residual effects.

It is believed that the composition of the invention forms one or more substantially discreet layers when applied to the skin. For example, the composition typically comprises a first hydrophobic film and a second outer film. Another layer can be present between these two layers that comprises active ingredients. For example, a layer of anionic moieties (from the fatty anionic surfactants) will typically coat the surface of the first hydrophobic film opposite the skin. Other active agents that precipitate from the composition before the second film forms can also form a layer between the first and outer films. Moreover, when the second film forms it can exclude other active agents that are still solubilized in the liquid carrier, and thereby form an additional layer on the outside of the outer film.

These layers will typically be substantially discreet. In many instances, however, various components of the composition will separate into different layers of the composition. This can happen, for example, if some of the ingredients that comprise the first film forming component are not incorporated in the film, or if some of the cationic surfactant does not end up between the first film and the skin.

In some compositions the separation of ingredients among layers can be done by design. This is especially true of compositions used to deliver medicinal agents to the surface of the skin. In such compositions the medicinal agent will preferably be at least partially soluble in the first film. Some compositions may, however, comprise more medicinal agent in the composition than can be solubilized by the film, and as a result the medicinal agent may separate among the layers of the composition.

Thus, the first film that eventually forms from the first film forming component can incorporate in its structure various of the other ingredients contained in the composition. Active agents, in particular, are often incorporated into the film in order to enhance the effectiveness of the active agent.

The compositions of the invention preferably are about neutral, and even more preferably slightly basic, with pH typically not exceeding about 8.5, 8.0, 7.8, or 7.5, and typically not below about 7.1 or 7.5. For example, compositions having a pH of from about 6.5 to about 8.0 are preferred. Compositions having a pH of from about 7.1 to about 7.5 are even more preferred.

In another aspect the invention provides a phase stable emulsion comprising one or more quaternary ammonium compounds; one or more nonionic surfactants; one or more fatty esters; one or more fatty alcohols; and optionally one or more highly polar compounds. In a particularly preferred embodiment the above components are present at a preferred ratio at the moment that the emulsion is formed. Components that are added to the composition after the emulsion has formed are not included in the ratio. The ratio of the sum of the moles of quaternary ammonium compounds, surfactants, and highly polar compounds to the sum of the moles of fatty esters and alcohols is preferably from about 0.8 to about 1.2. In an even more preferred embodiment the ratio is about 1.0.

Highly polar compounds that are included in the ratio include those compounds that are ionic or that have a dipole moment that exceeds the dipole moment of methanol. Highly polar compounds are typically added to increase the solubility of nonpolar compounds in polar solvents, although they can also be added as active agents. For example, polar compounds that contain sulfur are preferred when using the composition

to treat burns because they are a source of sulfur which is used to heal damaged skin. Highly polar compounds include, for example, dimethyl sulfone (MSM) or zinc sulfate.

In another aspect the invention provides a composition that is present in the form of an emulsion comprising a fatty phase, wherein the fatty phase comprises the one or more fatty acids discussed above. The fatty phase further comprises one or more of the glycerides discussed above, typically mono-, di-, or tri-, but preferably triglycerides, alkoxyglycerols, and alkyl glycerols, such as are in natural shark liver oil. The fatty phase optionally comprises one or more of the other fatty components discussed above such as the fatty esters and fatty alcohols. In a preferred embodiment for delivering medicinal active agents to the surface of the skin, the molar ratio of the one or more fatty acids to the one or more glycerides and other fatty components is from about 1:2 to about 3.5:1, even more preferably from about 1:1 to about 2.5:1, and still even more preferably the ratio is about 2:1. It has been found that a composition having fatty acids and glycerides within this range of ratios are exceptional for topically delivering active agents, and that the ratio can be varied depending upon the topical effect desired for a particular system.

The invention also provides a process for preparing suitable compositions. In one aspect the invention provides a process for preparing a phase stable emulsion comprising: forming an aqueous phase; forming a second phase comprising one or more fatty acids, and one or more fatty alcohols and/or one or more fatty esters; mixing the first and second phases to form an emulsion; and mixing an organic base with the emulsion; wherein: (a) the emulsion optionally comprises one or more quaternary ammonium compounds, one or more surfactants, and/or highly polar compounds; and (b) the ratio of the sum of the moles of quaternary ammonium compounds, surfactants, and highly polar compounds, to the sum of the moles of fatty esters and fatty alcohols is from about 0.8 to about 1.2, preferably about 1.0. The various components are as defined above. The emulsion is preferably formed at a temperature of from about 57 C to about 80 C, preferably about 70 C. Moreover, the organic base is preferably mixed with the emulsion at a temperature of from about 57 C to about 80 C, preferably about 70 C. The fatty ester(s) may optionally be added to the aqueous phase, although preferably they are included in the fatty phase.

The pH of the emulsion is preferably adjusted after the organic base is added to the emulsion to the pH levels discussed above, preferably from about 7.1 to about 7.8. Moreover, the emulsion can be stabilized with an emulsion stabilizer, such as a carbomer. One or more active agents may be added to the aqueous phase, the second fatty phase, or the emulsion, either before or after the emulsion is formed. In particular, the loading of certain active agents can be increased beyond a level at which an emulsion containing that active agent would normally be stable, by adding at least some of the active agent after the emulsion has been formed and preferably stabilized. This active agent loading procedure can be particularly important for providing the desired high concentrations of active agents such as lauricidin, chlorohexidine gluconate, dimethylsulfone, and other highly polar compounds. In a particularly preferred embodiment some or all of the active agents are cationic.

In another embodiment the invention provides a process for preparing a phase stable emulsion comprising: forming an aqueous phase; forming a second phase comprising one or more fatty acids, one or more fatty alcohols, and one or more fatty esters; mixing the first and second phases to form an emulsion at a temperature of from about 57 C to about 80 C; and mixing an organic base with the emulsion at a temperature of from about 57 C to about 80 C. In a particularly suitable embodiment the second phase comprises fatty acids at a molar ratio of fatty acids to glycerides and other fatty components of from about 1:2 to about 3.5:1, more preferably from about 1:1 to about 2.5:1, and most preferably about 2:1.

The compositions of this invention can also be characterized by the proportion of several components that are present in some of the most preferred formulations, including wax, propolis, fatty acids, fatty alcohols, glycerides, and quaternary ammonium compounds. Thus, in one embodiment, these components are present in the following weight percentages, based on the total weight of the composition:

1. Wax (which includes bees wax and other fatty esters): greater than about 0.05, or 0.1 wt.%, and/or less than about 5.0, 3.0, or 1.0 wt.%.
2. Propolis: zero, or greater than about 0.01, .025, .or .05 wt.%, and/or less than about 5.0, 3.0, or 1.0 wt.%.

3. Fatty acids: greater than about 0.5, 1.0, 2.0, or 3.0 wt.%, and/or less than about 15, 10, 8, and 6 wt.%.
4. Fatty Alcohols: greater than about 0.3, 0.5, 1.0, or 1.5 wt.%, and/or less than about 10, 8, or 6 wt.%.
5. Glycerides: greater than about 0.1, 0.5, or 0.9, and/or less than about 10, 8, and 6 wt.%.
6. Quaternary ammonium compounds: greater than about 0.1, 0.25, or 1.0, and/or less than about 12.0, 8.0, or 6.0 wt.%.

In one embodiment, these components are present in the following weight proportions:

1. Wax (which includes bees wax and other fatty esters): greater than about 0.1 or 0.4 parts, and less than about 2.0 or 1.0 parts.
2. Propolis: zero, or greater than about 0.025, and/or less than about 1.5 or 1.0 parts.
3. Fatty acids: greater than about 1.5 or 3.0 parts, and/or less than about 9 or 6 parts.
4. Fatty Alcohols: greater than about 0.3, 0.5, 1.0, or 1.5 wt.%, and/or less than about 10, 8, or 6 wt.%.
5. Glycerides: greater than about 0.1, 0.5, or 0.9, and/or less than about 10, 8, and 6 wt.%.
6. Quaternary ammonium compounds: greater than about 0.1 or 1.0, and less than about 8.0 or 6.0 parts.

The foregoing weight proportions apply to the composition before it is applied to the skin or tissue. Alternatively, because the applied lotion or creme (after the volatile components have evaporated) consists substantially of the foregoing components, the applied lotion or creme can be described by the foregoing proportions, based on the total of the foregoing ingredients equaling 100 wt.%.

Where possible, only highly purified ingredients should be used. For example, the fatty esters should be triple distilled when possible. Similarly, with the naturally occurring ingredients, unwanted compounds such as heavy metals may be removed if done so without destroying the desired properties of the natural molecules. Other compounds can,

of course, be substituted for the specific ingredients disclosed herein, as discussed in the preceding paragraphs and as understood by workers skilled in the art.

In another aspect of the invention, it has been found that under certain conditions of the above-described processes for preparing the compositions and/or phase stable emulsions of the invention, solid particles that can be termed fatty micro-spheres are formed. The fatty micro-spheres are typically approximately spherical particles having a diameter of less than about 0.2 mm, with at least a solid outer layer comprising at least some of the fatty components of the composition. The micro-spheres may have semi-solid or liquid interior domains, and may be at least partially aglomerated with other particles.. Without wishing to be bound by theory, it is believed that the formation of the fatty micro-spheres is related to, or derived from the partial or complete solidification of micelles, mixed micelles, or micelle-like structures containing surface active agents, with the lipophilic tails of the constituent molecules oriented toward the center and, and the polar, hydrophillic heads oriented at the periphery.

The formation of fatty micro-spheres may occur when certain ranges of the ratios of certain components of the compositions are maintained during certain phases of the process for the preparation of the compositions and/or emulsions of the invention. As described hereinabove, phase stable emulsions that may not contain fatty micro-spheres are formed when the ratio of the sum of the moles of quaternary ammonium compounds, surfactants, and highly polar compounds to the sum of the moles of fatty esters and alcohols is between about 0.8 to about 1.2. However, the desirable fatty micro-spheres are formed only over narrower ranges of the above-described ratio. Normally, fatty micro-spheres may form when the ratio is between about 0.9 to about 1.1. The ratio also effects the residual tackiness or stickiness of the compositions and/or emulsions, after they are applied to the skin or a wound. Stickiness decreases as the ratio of the sum of the moles of quaternary ammonium compounds, surfactants, and highly polar compounds, to the sum of the moles of fatty esters and fatty alcohols, becomes closer to 1:1. It is believed that the stickiness results from a decrease in the quality of the spheres formed. For example, if the ratio is greater than 1.05 or less than 0.95, spheres may form, but there is increasing stickiness as the ratio drifts further outside that range. More preferably, the ratio is less

than about 1.01, and greater than about 0.99. It has been found that when the ratio is about 1.0000, almost no residual stickiness is observed after 30 seconds of rubbing the sphere-containing compositions onto the skin.

It is to be understood that the above-described surfactants include both non-ionic surfactants, and the anionic surfactants created by the neutralization of fatty acids, to give salts of fatty carboxylates, during the processes for preparing the compositions and/or phase stable emulsion, as described above and below. Accordingly, it has also been found that the fatty micro spheres form in the compositions and/or phase-stable emulsion only within certain pH ranges. A pH above about 8.5 reduces the number of fatty micro-spheres formed, and a minimum pH must be maintained that is effective to complete neutralization of the fatty acids, and form the fatty micro-spheres. A pH of about 5.5 or greater is sufficient to assure complete neutralization of typical fatty acids. Thus, fatty micro-sphere formation is typically favorable over a pH range from about 5.5 to about 8.5. In preferred embodiments, pH is from about 6.5 to about 8.0. In preferred embodiments, pH is from about 7.0 to 7.8 during the process for producing the fatty micro-spheres, with the result that stable, substantially uniform fatty micro-spheres are formed.

It is also believed that the formation and quality of the fatty micro-spheres formed is a function of the temperature at which the neutralization of fatty acids occurs. Fatty micro-spheres do not typically form if the neutralization is carried out at temperatures of less than about 55°C or more than about 100°C. A more preferred temperature range for the neutralization is from about 65°C to about 90°C and the most preferred temperature range is from 70°C to about 85°C.

While not wishing to be bound by theory, it is believed that fatty micro-spheres form as the fatty components begin to solidity within the micelles, mixed micelles, or micelle-like structures formed in the compositions and/or phase-stable emulsions of the invention, as their temperature is lowered. Those of skill in the art will recognize that the temperature at which fatty micro-spheres form is a complex function of the identity and quantities of the chemical components of the compositions and/or phase stable emulsions. In certain preferred embodiments described herein, fatty micro-sphere formation begins

at about 55.5°C, and is substantially complete at about 54.9°C. Once formed, the fatty micro-spheres are remarkably stable.

Therefore the invention relates, in one aspect, to a process for preparing a composition or phase stable emulsion having fatty micro-spheres therein, comprising

a. mixing in any sequence:
   i. one or more active agents;
   ii. a nonionic or substantially nonionic first film forming component comprising at least one fatty ester or fatty alcohol;
   iii. one or more cationic surfactants comprising a quaternary ammonium compound that is substituted with one or more lower alkyl moieties and one or more fatty moieties comprising from 16 to 22 carbon atoms, that are soluble in the first film forming component;
   iv. one or more fatty acids;
   v. optionally one or more highly polar compounds;
   vi. optionally one or more non-ionic surfactants; and
   vii. a liquid carrier;

   wherein the mole ratio of the sum of the fatty acids, non-ionic surfactants, quaternary ammonium compound, and highly polar compounds, divided by the sum of the fatty esters and fatty alcohols is from about 0 .9 to about 1.1;
b. neutralizing the fatty acids with an organic base to a pH effective to complete neutralization of the fatty acids; and
c. cooling the neutralized composition to a temperature effective to form a composition having at least some fatty micro-spheres.

Optionally the compositions and/or phase stable emulsions are agitated during the process of forming the fatty micro-spheres, by any suitable means of agitation known to those of skill in the art. If the process is not agitated, fatty micro-spheres typically form, but their size distributions and quality are not as uniform as when agitation is employed.

In certain preferred embodiments of the processes of the invention, unexpectedly uniform and high quality fatty micro-spheres form when the ratio the sum of the moles of quaternary ammonium compounds, non-ionic surfactants, neutralized fatty acids, and highly polar compounds, to the sum of the moles of fatty esters and fatty alcohols is about 1.000, the neutralization of the fatty acids occurs between about 70°C and about 85°C, the pH is between about 7.0 to about 7.8, and agitation is employed during the formation of the fatty micro-spheres.

In some embodiments of the above-described process, formation of the fatty micro-spheres produces a thickening and/or increase in the inherent viscosity of the composition or phase stable emulsion. Any undesirable thickening or viscosity increase may be reduced if desired, by incorporating air or other gases into the composition while optionally agitating.

Active agents, and/or some or all of certain ingredients can be added before or after the formation of the fatty micro-spheres. In certain embodiments in which the ingredients and/or active agents are added before the formation of the fatty micro-spheres, it is believed that the chemical ingredients and/or active agents distribute themselves within the fatty micro-spheres and the remaining substantially aqueous medium (the "gravy") as determined by the chemical and physical characteristics of the ingredients and/or active agents. When present during the formation of the fatty micro-spheres, it is believed that the ingredients and/or active agents distribute themselves within the interior of the fatty micro-spheres in a substantially uniform way. The concentration of water-soluble ingredients may be the same or different within the fatty micro-spheres as compared to the surrounding watery fluid, at the time of micro-sphere formation.

In certain other embodiments of the processes of the invention , additional ingredients and/or active agents are added after the formation of the fatty micro-spheres. Stated alternatively, once the fatty micro-spheres are formed and/or solidified, additional ingredients and/or active agents can be added to the composition. In many cases, the additional ingredients and/or active agents may not fully penetrate or become incorporated into the fatty micro-spheres, and may be preferentially retained in the substantially aqueous medium surrounding the fatty micro-spheres. This can provide a clinically important

benefit, because certain water-soluble materials and/or active agents can be artificially concentrated in the substantially aqueous medium, as compared to the fatty micro-spheres. As a result, when a wound site is treated with the fatty micro-sphere containing compositions, the wound is initially bathed with a relatively highly concentrated aqueous dose of the additional ingredient and/or active agent, followed by a less concentrated dose when the spheres are later absorbed by the wound.

It is to be understood that if an additional ingredient and/or active agent is added after the formation of the fatty micro-spheres, the additional ingredient and/or active agent added is not included in the above described preferred ratios (of the sum of the moles of quaternary ammonium compounds, surfactants, and highly polar compounds, to the sum of the moles of fatty esters and fatty alcohols). This addition technique can be employed to produce non-tacky, high quality micro-spheres, yet allow considerable flexibility in the permissible overall concentration of any potentially ratio-impacting ingredient, by permitting selective addition of some or all of the potentially ratio-impacting ingredient to the gravy, rather than the fatty micro-spheres. For example, in one of the embodiments of the invention, it is desired to add Vitamin E acetate (a fatty ester that would normally be counted in the ratios) to a desired high level. If the total desired quantity of Vitamin E acetate is added prior to the formation of the fatty microspheres, the ratio is 0.9642, and a relatively sticky product is obtained. However, if the Vitamin E acetate is added after the formation of the fatty micro-spheres, the Vitamin E acetate is not counted when satisfying the preferred ratios, so that a product that is not sticky after 30 seconds of rubbing may be produced, and yet there are no other changes in the efficacy of the product.

In another related embodiment, an additional ingredient or active agent having a melting temperature above room temperature, but below the temperature of formation of fatty microspheres can be added to a previously formed composition containing fatty micro-spheres. When the additional ingredient or active agent melts, a substantial thinning, or decrease in the viscosity of the solution is observed. Nevertheless, as further cooling progresses, the additional ingredient or active agent may crystallize, again thickening or increasing the viscosity of the composition produced. Moreover, the crystal size of the reformed crystals of the additional ingredient or active agent can be

manipulated. By employing agitation during the additional cooling, the crystals of the ingredient or active agent formed can be relatively small, numerous, have high surface area, and therefore re-dissolve quickly upon application. Without agitation, the crystals may become large, have relatively limited surface area and be slow to dissolve. When said crystals are an active agent, the dissolution rate of the large crystals formed can be reduced to provide controlled release of the active agent.

For example, spheres may be substantially completely formed in one of the inventive phase stable emulsion compositions at 54.9°C. A blue dye is added and the background color of the "spheres and gravy" composition is the color of mustard. Then povidone iodine (an anti-septic active agent having a deep rust color) is added. The povidone iodine melts and causes the apparent viscosity of the composition to decrease, and become thoroughly mixed. The resulting mixture is the color of pea soup. The mixture is allowed to cool to room temperature over at least about 4 hours, (preferably at least about 24 hours, more preferably at least about 48 hours). Optionally, the cooling takes place in a substantially sealed vessel. Cooling in an unagitated substantially sealed vessel reduces the rate of cooling and makes larger, more uniform povidone iodide crystals. After cooling, the product is agitated by incorporation of air for three minutes, such that the specific gravity is reduced from about .98 to about .91. This mix is now a lemon-lime green with rust colored speckles. With additional aging, the rust colored speckles disappear. Under a microscope, the reformed povidone iodine crystals are coated with green "gravy", obscuring their true color. Upon application of the anti-septic composition, the intentionally large and slow-to-dissolve povidone iodide crystals release iodine active agent over an extended period of time of up to three to four hours, extending the duration of anti-septic efficacy.

In another example, Triclosan is an anti-septic active agent reported to melt above the temperature of fatty micro-sphere formation. Surprisingly, the Triclosan appears to melt or dissolve at temperatures below the sphere formation temperature. After about one minute of mixing, the viscosity of the mixture suddenly drops and turns the color of mustard. The melt is allowed to cool to room temperature over at least 4 hours. Cooling in an unagitated substantially sealed vessel reduces the rate of cooling and results in larger,

more uniform crystals. After cooling, the product is agitated by incorporation of air for three minutes, such that the specific gravity is reduced and has a bright yellow color. Upon application of the anti-septic composition, the large and slow-to-dissolve crystals meter Triclosan active agent to the skin over an extended period of time, extending the duration of anti-septic efficacy.

In yet another embodiment of the above described process, additional ingredients, optically fluorescent or phosphorescent compounds, and/or other active agents may be mixed with the composition or phase stable emulsion after the formation of the microspheres. Preferably, the additional ingredients and/or active agents are melted or dissolved into the composition or phase stable emulsion, to form a modified composition containing fatty micro-spheres, then the resulting modified composition is further cooled to at least partially crystallize the additional ingredient and/or active agent. Optionally, the modified composition may be agitated or it's cooling rate controlled so as to modify the crystal size of the additional ingredient and/or active agent.

In some embodiments of the applications of the instant compositions, at least two different compositions within the scope of the invention are separately applied to the same area of the skin or body, to form a layered coating on the body. For example, in one embodiment, a composition according to the invention having few or no active ingredients is first applied to the hands and allowed to dry. The resulting substantially dry base coat seals and protects the skin from direct contact with potentially irritating ingredients or active agents. In a subsequent step, a composition within the scope of the invention having ingredients or active agents, including those designed to form a sealing barrier film is applied to the same, previously coated, area of the skin. Film- forming ingredients that are effective to form such sealing barrier films include polymeric substances such as Polyderm CO, PE and SA (available from Akzo Chemical Co., Sayreville, NJ) and the like. Further layers of the compositions of the invention, containing other active agents may be applied if desired. The resulting multi-layer layered coating structure on the hands is non irritating and impervious to aggressive industrial chemicals such as paint, solvents acids and the like. Such a multi step process is particularly useful in protecting workers hands who work in the petroleum, petrochemical and chemical industries.

Experimental

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts per 100 parts total weight of the final composition, which is equivalent to weight percent of the final composition, temperature is in °C. or is at room temperature, and pressure is at or near atmospheric. Listed compounds are commercial grade.

Example 1

An aqueous phase was first prepared by mixing the following components in the weight proportions listed. The aqueous phase was heated to 70 C and mixed until creamy and uniform.

NAME OF INGREDIENT	WEIGHT %
D.I. water	63.14
Merquat 550 Polyquaternium-7	1.150
Dimethyl Distearyl Ammonium Chloride	1.300
Berberine Hydrochloride	0.013
Active Agents	4.75

A fatty phase was next prepared by mixing the following components in the weight proportions listed, and heating the mixture to 70 C. 0.500 weight % lemon oil were then added to the mixture. The fatty phase thus formed was then added to the aqueous phase, and mixed until uniformly consistent. Temperature was maintained at 70 C.

NAME OF INGREDIENT	WEIGHT%
Stearic Acid	3.750
Cetyl Alcohol	2.955

Lauricidin	3.150
Propolis	0.400
Crude Bees Wax	1.000
Other Active Agents	3.450

A third mixture was then prepared by combining the following ingredients at the weight proportions listed, at ambient temperature. The third mixture was then combined with the above mixture under high shear agitation to form an emulsion, with the temperature maintained at 70 C.

NAME OF INGREDIENT	WEIGHT %
D.I. Water	3.000
TEA	1.540
Tetra Na EDTA (solid)	0.300

The emulsion was allowed to cool to 50 C, and 4.53 weight %of processing aids were mixed with the emulsion. 2.5 weight % of other active agents were then added to the emulsion (including 0.25 % chlorohexidine gluconate), and the pH was lowered to about 7.4 with citric acid.

Example 2

An emulsion was formed substantially following the procedure of Example 1. The aqueous phase contained:

NAME OF INGREDIENT	WEIGHT %
Water	65.01
Dimethyl Sulfone	0.830
Dimethyl Distearyl Ammonium Chloride	4.500
Active Agents	3.683

The fatty phase contained:

NAME OF INGREDIENT	WEIGHT %
Stearic Acid	4.421

Cetyl Alcohol	4.119
Crude Bees Wax	0.900
Propolis	0.750
Lauricidin	3.840
Glycerides	3.993
Cetyl Lactate	0.250
Ascorbyl Palmitate	0.150
Active Agents	0.575

4.66 weight % of processing aids were added to the mixture. 2.319 weight % of triethanolamine were then added to the mixture to adjust the pH to 6.9.

Example 3

This example illustrates the preparation of an emulsion suitable for application to children's skin. An emulsion was formed substantially following the procedure of Example 1. The aqueous phase contained:

NAME OF INGREDIENT	WEIGHT %
D.I. Water	80.29
Berberine hydrochloride	0.05
Dimethyl Distearyl Ammonium Chloride	0.25
Active Agents	0.35

The fatty phase contained:

NAME OF INGREDIENT	WEIGHT %
Stearic Acid	3.0
Cetyl Alcohol	1.7
Crude Bees Wax	0.5
Propolis	0.1
Lauricidin	0.98
Ascorbyl Palmitate	0.2
Active Agents	0.15

The quantity of lauricidin added to the fatty phase was sufficient to balance the critical mole ratios for the formation and stability of the emulsion. 7.85 weight % of processing aids, (including a carbomer and propylene glycol) were added to the mixture. 1.35 weight % of triethanolamine were then added to the mixture to form the emulsion and adjust the pH to 7.1, to enhance the protection of tender young skin.

Additional lauricidin (3.15 weight %) was added after the emulsion was formed and stable, to provide the safe and non-toxic anti-microbial activity needed, but not disrupt the phase stability of the emulsion.

Example 4

This example illustrates the preparation of an emulsion suitable for application to children's skin. An emulsion was formed substantially following the procedure of Example 1. The aqueous phase contained:

NAME OF INGREDIENT	WEIGHT %
D.I. Water	80.29
Berberine hydrochloride	0.02
Dimethyl Distearyl Ammonium Chloride	0.1
Active Agents	0.35

The fatty phase contained:

NAME OF INGREDIENT	WEIGHT %
Stearic Acid	3.0
Cetyl Alcohol	1.7
Crude Bees Wax	0.4
Propolis	0.1
Lauricidin	0.895
Glycerides	0.65
Ascorbyl Palmitate	0.2
Active Agents	0.15

The quantity of lauricidin added to the fatty phase was sufficient to balance the critical mole ratios for the formation and stability of the emulsion. 6.60 weight % of processing aids (including a carbomer and propylene glycol) were added to the mixture. 1.25 weight % of triethanolamine and 0.1 weight % of tetra-sodium EDTA were then added to the mixture to form the emulsion and adjust the pH to 6.8, to enhance the protection of tender young skin.

Additional lauricidin (3.485 weight %) was added after the emulsion is formed and stable, to provide the safe and non-toxic anti-microbial activity needed, but not disrupt the phase stability of the emulsion.

Example 5

An emulsion was formed according to Example 1, except that chlorohexidine gluconate (CHG) was added at 0.69 weight % (on an active basis, using a 20% aqueous solution of CHG). The subsequent emulsion was low in viscosity, and caused a perception of an unpleasant rush of blood to the hands. Users feared their hands would be hurt with continued use.

Accordingly, in an improved procedure, the Example 1 emulsion was prepared (except for a lowering of water, to compensate for water to be added later with the CHG) , but the 0.69 weight % of CHG was added after the emulsion was stable and cooled to 50 °C. The emulsion prepared by the improved procedure had good viscosity, and eliminated the perception of blood rush to the hands.

Example 6

This example illustrates the preparation of a neutral emulsion having only a small quantity of active agents and non-ionic surfactants, suitable for application to damaged, irritated or bleeding skin. Such emulsions are typically applied as a base coat on damaged skin prior to applying an emulsion having potentially irritating agents, such as the CHG in the emulsion of Example 1. An emulsion was formed substantially following the procedure of Example 1. The aqueous phase contained:

NAME OF INGREDIENT	WEIGHT %
D.I. Water	64.47
Dimethyl Distearyl Ammonium Chloride	4.50
Dimethylsulfone	0.636
Active Agents	0.60

The fatty phase contained:

NAME OF INGREDIENT	WEIGHT %
Stearic Acid	3.91
Cetyl Alcohol	3.50
Lauricidin	4.00
Glycerides	3.422
Active Agents	0.15

11.36 weight % of processing aids were added to the mixture (including a carbomer stabilizer and propylene glycol). 3.1 weight % of triethanolamine and 0.1 weight % of tetra-sodium EDTA was then added to the mixture to form the emulsion and adjust the pH to 7.1.

Example 7

This example illustrates the preparation of a composition for removing warts. An emulsion was formed substantially following the procedure of Example 1. The aqueous phase contained:

NAME OF INGREDIENT	WEIGHT %
D.I. Water	58.23
Dimethyl Distearyl Ammonium Chloride	2.50
Dimethylsulfone	1.0
Merquat 550	1.15
Berberine Hydrochloride	0.30
Zinc Sulfate	0.20
Arabino Galactan	0.25
Triton X-100	1.0

Nonoxynol-9	1.0
Pyrolidine Carboxylic Acid	0.2
Poly oxy 10	2.0
Aloe Vera	0.25

The fatty phase contained:

NAME OF INGREDIENT	WEIGHT %
Stearic Acid	4.1
Cetyl Alcohol	3.82
Lauricidin	3.80
Crude Bees Wax	0.4
Propolis	0.2
Allantoin	0.3
Lemon Oil	0.8
Vitamin E Acetate	0.4
Ascorbyl Palmitate	0.2
Glyceryl decanoate	0.5
Neem Oil	0.758
Shark Liver Oil	2.50
Eicosapentaenoic Acid	0.36
Conjugated Linoleic Acid	0.36
Gamma Linolenic Acid	0.36
Tetra Na EDTA	0.3
Triethanolamine	1.724
Carbomer 940 NF	0.12
Propylene Glycol	3.5

A third mixture of 3 weight % water, 1.724 weight % triethanolamine, and 0.3 weight % tetra-sodium ethylene diamine tetraacetic acid was formed, then mixed with the aqueous and fatty phases at 70 °C to form the emulsion. The emulsion was cooled to 55 °C, and mixture of 3.5 weight % water, 0.12 weight % Carbomer 940 NF, 3.5 weight % propylene glycol, and 0.755 weight % of the dimethylsulfone, were added to the emulsion. The emulsion was cooled to 50 °C, and 0.1 weight % of Boswellin, 0.3 weight % of NDHA, 0.3 weight % of Tomatine, 0.01 weight % Vitamin A, 0.1 weight % of Vitamin D, and 0.2 weight % of Lycopene were mixed with the emulsion.

Example 8

This example illustrates the preparation of a composition for treating burns. An emulsion was formed substantially following the procedure of Example 1. The aqueous phase contained:

NAME OF INGREDIENT	WEIGHT %
D.I. Water	59.825
Dimethyl Distearyl Ammonium Chloride	4.7
Dimethylsulfone	0.83
Merquat 550	1.15
Triton-X-100	0.0
Tomatine	0.30
Boswellin	0.10
Arabino Galactan	0.25
Active Agents	2.79

The fatty phase contained:

NAME OF INGREDIENT	WEIGHT %
Stearic Acid	4.1
Cetyl Alcohol	3.82
Lauricidin	4.00
Crude Bees Wax	0.9
Propolis	0.3
Other Active Agents	5.203

A third mixture of 3 weight % water, 1.577 weight % triethanolamine, and 0.4 weight % tetra-sodium ethylene diamine tetraacetic acid was formed, then mixed with the aqueous and fatty phases to form the emulsion. A mixture of 3.0 weight % de-ionized water, 4.42 weight % process aids (including a carbomer stabilizer), 0.21 weight % dimethylsulfone, and 0.275 weight % of Active ingredients were then mixed with the emulsion.

Example 9

This example illustrates the preparation of another composition for treating burns. An emulsion was formed substantially following the procedure of Example 1. The aqueous phase contained:

NAME OF INGREDIENT	WEIGHT %
D.I. Water	50.068
Dimethyl Distearyl Ammonium Chloride	4.7
Dimethylsulfone	0.597
Active Agents	3.44

The fatty phase contained:

NAME OF INGREDIENT	WEIGHT %
Stearic Acid	4.1
Cetyl Alcohol	3.82
Lauricidin	3
Squalene	0.6
Ascorbyl Palmitate	0.26
Other Surfactants	0.6
Other Active Agents	5.385

The aqueous and fatty phases were mixed, then a third mixture of 3 weight % water, 1.577 weight % triethanolamine, and 0.4 weight % tetra-sodium ethylene diamine tetraacetic acid was added to the aqueous and fatty phases at 70 °C to form the emulsion. The emulsion was cooled to 55 °C, and 3.0 weight % de-ionized water, 8.92 weight % process aids (including a carbomer and propylene glycol), 0.403 weight % dimethylsulfone, and 5.86 weight % of Active ingredients was mixed with the emulsion. The emulsion was then cooled to 50 °C, and then another 0.4 weight% of active ingredients were added to the stabilized emulsion.

Examples 10-14

These examples illustrate compositions for treating burns and skin lesions. The emulsions were formed substantially following the procedures described above. The final compositions contained :

Example #	10	11	12	13	14
Application of Composition	**Deep Wounds**	**Surface Wounds**	**Thermal Burns**	**Radiation Burns**	**Deep Wounds**
Name of Ingredient	Wt %	Wt %	Wt %	Wt %	Wt%
Water	60.364	70.06	67.67	70.796	63.25
Dimethyl Distearyl Ammonium Chloride	4.5	4.5	4.5	4.5	4.5
Aloe Vera	0.250	0.100	0.250	0.400	0.300
Allantoin	0.600	0.150	0.500	0.300	0.300
Ferulic Acid	0.080	0.050	0.080		0.100
Dimethylsulfone (Pre-emulsion)	0.817	0.700	0.761	0.830	0.647
Pyrolidine Carboxylic Acid	0.200	0.200	0.100	0.200	0.200
Dimethyl Benzethonium Chloride	0.250	0.500	0.250	0.250	0.250
Colostrum	0.200	0.200	0.200	0.300	0.300
Lipoic Acid	0.050	0.050	0.080	0.080	0.080
Bilberry	0.200				
Grape Seed Extract	0.100	0.200	0.200	0.400	0.300
Zinc Methionone	0.200		0.100	0.200	0.200
Zinc Sulfate	0.100	0.200	0.100	0.200	0.200
Silica Gel	0.100	0.100	0.050	0.100	0.100
Bioperine	0.080	0.080	0.080	0.080	0.080
Arginine	0.300	0.250	0.250	0.300	0.300
Proline	0.100	0.100	0.100	0.100	0.100
L-Glutamine	0.100		0.100	0.100	0.400
Trimethyl Glycine			0.100		
Glycine			0.100		
Cu-Curcumin	0.100			0.100	0.050
Glycyrrhizic Acid				0.050	0.050
Glucosamine HCI				0.100	0.100
Natural Honey					0.200
RNA				0.100	0.100
Inositol	0.200				
Boswellin		0.150			
Berberine HCI		0.050			
Dexpanthenol	0.330	0.330	0.630	0.330	0.330
Phytantriol	0.110	0.110	0.315	0.110	0.110
Tetra Sodium EDTA	1.250	0.750	1.250		

Polysorbate-80	.200	0.100	0.300	0.040	
Symphytum			0.025		
Stearic Acid	4.100	4.128	4.100	4.100	4.100
Cetyl Alcohol	3.820	3.820	3.820	3.820	3.820
Crude Beeswax	0.900	0.900	0.900	0.600	0.600
Lauricidin	3.800	3.700	4.000	4.000	3.800
B-Carotene - 95%				0.016	
Ascorbyl Palmitate	0.200	0.150	0.150	0.200	0.200
Neem Oil	0.300	0.300	0.400	0.495	0.514
Shark Oil	2.310	2.000	1.592	3.300	2.000
Conjugated Linoleic Acid	0.400	0.400	0.484	0.315	0.400
Eicosapentaenoic Acid	0.500	0.500	0.484	0.315	0.500
Lemon Oil	0.200	0.400	0.200	0.200	0.200
Pregnenolone	0.200	0.200	0.200		
Dihomo Gamma Linolenic Acid	0.100	0.100	0.100	0.100	0.100
Cetyl Lactate	0.250	0.250			
Gamma Linolenic Acid	0.400	0.400	0.484	0.315	0.400
B-Carotene - 95%	0.016	0.002	0.0160	0.188	0.002
Propolis	0.200	0.300	0.300	0.025	0.025
Water	0.000	0.00			
Triethanolamine	12.400	5.163	5.500	5.400	
Propylene Glycol	4.000	3.500	4.000	4.000	4.000
Water	0.000	0.00			2.000
Carbomer 980 NF	0.500	0.500	0.500	0.500	
Carbomer 940 NF					0.080
Glycerin	0.300	0.300	0.300	0.300	0.300
Vitamin A	0.002	0.002	0.002	0.002	0.002
Vitamin D	0.002	0.002	0.002	0.002	0.002
Vitamin K	0.002	0.002	0.002	0.002	0.002
Vitamin E	0.150	0.150	0.150	0.250	0.250
B-Carotene - 95%	0.188	0.011			
Vanilla Extract	0.050	0.060	0.050	0.050	0.050
Tocotrienol	0.080	0.080	0.080	0.080	0.080
Pregnenolone				0.200	0.200
Lycopene	0.100		0.100	0.300	0.100
Dimethylsulfone (Post Emulsion)			0.239		
Tetra Na EDTA				0.400	0.400
Water					1.750
Triethanolamine to give pH 6.9±.1					1.577

Example 15

A product having the composition of Example 10 was used to treat a wound on a patient's heel that had resisted healing for over six weeks. Two to three times per

day the open wound was packed with the product and covered with gauze. The length, width, and depth of the wound were measured approximately weekly, and the estimated volume of the wound was calculated and plotted versus time, as shown in Figure 1.

Example 16

A nurse dropped a hot curling iron between her breasts while dressing, causing a severe burn. The nurse subsequently applied a product having the composition of Example 12 to the burn. Not only did the burn heal completely, but no scar tissue was formed in this sensitive area.

Example 17

Radiation burns are often a byproduct of radiation treatment of cancer. A product having the composition of Example 13 was applied topically to the skin of predetermined site of radiation treatment for a cancer patient before the radiation treatment. No burn was apparent after radiation therapy, and the attending physician described the non-event as "extraordinary".

Example 18

The following protocol is used to prevent radiation-induced dermatitis and related skin injury using, for example, the composition of Example 13. Following the procedures for application carefully will ensure successful completion of radiation therapy without injury to the overlying skin and tissue:

1. Apply composition to areas marked for radiation therapy. Apply one (1) hour before radiation therapy.
2. Reapply immediately after radiation therapy.
3. Technique for application:
    a. With a clean cotton swab or a tongue blade, apply thin layer or coating to cover completely the marked areas for radiation therapy;
    b. Wait fifteen (15) seconds;
    c. Then, with a clean fingertip, rub into skin until fully absorbed.

Example 19

The following protocol is used to maintain the skin in a healthy state during and after radiation therapy and will help prevent skin infections and other tissue damage from developing using, for example, the composition of Example 13.

1. Apply twice daily, on day of therapy - two (2) or four (4) hours after last application of composition of Example 13, and at bedtime.
2. On off days (no radiation therapy), apply three (3) times (morning, noon and night).
3. Technique for application is the same as described above for Example 18.
4. Wait fifteen (15) seconds, then rub into skin.

Example 20

The following protocol is used to treat first, second, and third degree burns, using, for example, the compositions of Examples 10 & 11. Carefully following the procedures, full application will ensure successful healing with limited scarring at the burn site. Should any signs of localized or systemic infection occur, then aggressive antibiotic therapy is indicated and should be started immediately.

Initial Assessment of Burns

Emergent phase (0 to 72 hours post-burn). Clinical assessment and complete history and physical are critical during this phase of treatment.

1. Rule of nines is the easiest way to assess the extent of burn in adults.
2. Depth of burns.
    a. Partial thickness (intradermal) - these injuries may appear red or pink, often with blister formation;
    b. Full thickness - these injuries may be charred or marble-gray in color, dry and anesthetic;
    c. Partial thickness burns may also have some anesthesia at times due to nerve endings being injured so the pain response is useful only when positive indicating a partial thickness burn.

Directions for Use

1. Apply to entire area of burn with some overlap onto normal tissue to ensure that all unrecognized burned tissue is covered (early in the course of a burn, the area of burn may be underestimated).
2. Apply immediately or as soon as possible to the burned areas after estimates of percent of burn and degree of burn are completed.
3. Apply two (2) to three (3) times per day.
4. Cover the treated burn with one (1) layer of flexible gauze-like conform, etc.
5. Debridement is not necessary, and in some embodiments may be avoided during one or more applications, but will generally occur with the dressing change. More extensive debridement of blisters or eschar should be done as is clinically indicated.
6. Continue applications until patient is healed.

Example 21

The following protocol is useful for treating stage 1, stage 2, stage 3, or stage 4 wounds, using the composition set forth in Example 11 (for stage 1 and stage 2 wounds) and Examples 10 and 14 (for stage 3 and stage 4 wounds). The antibiotic concentration for stage 1 and stage 2 wounds is greater typically to allow penetration through the epidermis and dermis and superficial wounds.

Classifications

Stage 1:	Red, unbroken skin, no blanching.
Stage 2:	Blistered or broken skin. Wound base moist and pink. Free of necrotic tissue.
Stage 3:	Extends through the dermis to involve subcutaneous tissue.
Stage 4:	Deep tissue destruction extending through subcutaneous tissue, may involve muscle layers, joint and/or bone. Present as a deep crater. May include necrotic tissue.
Note:	Any wound with eschar cannot be properly staged and should be classified as a full thickness wound.

Directions for Use

1. Make all appropriate measurements of size, and dimensions of erythema and eschar.
2. Culture wound.
3. Debride wound if necessary.
4. Make accurate assessment of depth using a sterile swab and measuring the depth from the swab.
5. For stage 1 and stage 2 wounds, apply a thin coat of the composition to the wound and let stand for 30 seconds. Then, topically run the formula into the skin observing the oxidation effect.
6. For stage 3 and greater wounds, apply the composition making sure to completely fill the wound, including any voids, channels, or cavities in the tissue or walls of the wound, to slightly above epidermal level.
7. Cover the wound with one (1) layer of gauze bandage and wrap with conform to keep the areas of tunneling or undermining fully saturated and dressings intact.
8. Change dressings two (2) or three (3) times daily, repeating this process.

Notes

1. It is not necessary to use any microbial cleaners during the healing process. Irrigating with normal saline may be appropriate.
2. If there appears to be evidence of topical wound infection that stays localized and does not extend greater than 0.5 to 1.0 centimeters beyond the wound margin and the patient does not become febrile, then proceed with the application as prescribed. The topical infection characteristically remits within 12-36 hours. If the patent becomes febrile or if there is a question of cellulitis, then proceed with vigorous systemic antibiotic therapy in addition to the treatment.
3. If significant eschar formation is present, debridement is indicated prior to initial treatment. Characteristically, the appropriate treatment will soften the

eschar formation and gently lift this to extrusion as part of the healing process in three (3) to six (6) days if sharp and blunt disection is not readily available.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

1. A process for preparing a composition or phase stable emulsion having fatty micro-spheres therein, comprising:
   a) mixing in any sequence:
      i) one or more active agents;
      ii) a first film forming component comprising at least one fatty ester or at least one fatty alcohol;
      iii) one or more cationic surfactants comprising a quaternary ammonium compound that is substituted with one or more fatty moieties comprising from 16 to 22 carbon atoms;
      iv) one or more fatty acids;
      v) optionally one or more highly polar compounds;
      vi) optionally one or more non-ionic surfactants; and
      vii) a liquid carrier;

      wherein the mole ratio of the sum of the fatty acids, non-ionic surfactants, quaternary ammonium compounds, and highly polar compounds, divided by the sum of the fatty esters and fatty alcohols is from about 0.9 to about 1.1;
   b) neutralizing the fatty acids with an organic base at a temperature of greater than about 55 °C; and
   c) cooling the neutralized composition to form a composition having at least some fatty micro-spheres.

2. The process of claim 1, wherein the mole ratio of the sum of the fatty acids, non-ionic surfactants, quaternary ammonium compound, and highly polar compounds, divided by the sum of the fatty esters and fatty alcohols is from about 0 .95 to about 1.05.

3. The process of claim 1, wherein the mole ratio of the sum of the fatty acids, non-ionic surfactants, quaternary ammonium compound, and highly polar compounds, divided by the sum of the fatty esters and fatty alcohols is from about 0 .99 to about 1.01.

4. The process of claim 1, wherein the pH after neutralization is from about 5.5 to about 8.5.

5. The process of claim 1, wherein the pH after neutralization is from about 7.0 to about 7.8.

6. The process of claim 1, wherein the neutralization of the fatty acids occurs at a temperature from about 55 °C to about 100 °C.

7. The process of claim 1, wherein the neutralization of the fatty acids occurs at a temperature from about 70 °C to about 85 °C.

8. The process of claim 1, wherein the ratio the sum of the moles of quaternary ammonium compounds, non-ionic surfactants, neutralized fatty acids, and highly polar compounds, to the sum of the moles of fatty esters and fatty alcohols is about 1.000, the neutralization of the fatty acids occurs between about 70°C and about 85°C, the pH is between about 7.0 to about 7.8, and agitation is employed during the formation of the fatty micro-spheres.

9. The process of claim 1, wherein one or more ingredients or active agents is added after the formation of the microspheres.

10. The process of claim 9, wherein at least one of the ingredients or active agents added after the formation of the microspheres crystallizes upon further cooling.

11. The process of claim 1, wherein the organic base is triethanolamine, tromethamine, or tetrasodium EDTA.

12. The process of claim 1, wherein agitation is employed during the formation of the fatty microspheres.

13. The process of claim 1, wherein the composition is agitated after the formation of the product to incorporate air.

14. The process of claim 1, wherein the liquid carrier comprises water.

15. The process of claim 1, wherein the first film forming component further comprises one or more glycerides or other fatty components.

16. The process of claim 15, wherein the molar ratio of the one or more fatty acids to the one or more glycerides,is from about 1:1 to about 2.5: 1.

17. The composition or phase stable emulsion produced by the process of claim 1.

18. The composition or phase stable emulsion of claim 17 wherein the fatty micro-spheres are approximately spherical particles having a diameter of less than about 0.2 mm and a solid outer layer.

19. The composition or phase stable emulsion of claim 18 wherein the solid outer layer comprises one or more fatty esters, one or more fatty alcohols, one or more neutralized fatty acids, or a mixture thereof.

20. The composition or phase stable emulsion of claim 19, wherein the fatty microspheres comprise a semi-solid or liquid interior domain.